

Exposure to selected fragrance materials

A case study of fragrance-mix-positive eczema patients

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The aim of the present study was to assess exposure to constituents of the fragrance mix from cosmetic products used by fragrance-mix-positive eczema patients. 23 products, which had either given a positive patch and/or use test in a total of 11 fragrance-mix-positive patients, were analyzed. In all cases, the use of these cosmetics completely or partly explained present or past episodes of eczema. Between 1 to 6 constituents of the fragrance mix were found in 22 out of 23 products. The cosmetics of all the patients sensitive to hydroxycitronellal, eugenol, cinnamic alcohol and α -amylcinnamic aldehyde were found to contain the respective substances. Exposure concentrations were seen to cover a large range. The content of hydroxycitronellal was, on average, 5× higher in cosmetics from hydroxycitronellal-sensitive patients, compared to cosmetics from hydroxycitronellal-negative patients. It is concluded that exposure to constituents of the fragrance mix is common in fragrance-allergic patients with cosmetic eczema, and that the fragrance mix is a good reflection of actual exposure.

Key words: fragrance mix; constituents; cosmetic allergy; exposure concentrations; relevance of patch test reactions © Munksgaard, 1996.

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Fragrance materials are one of the major causes of allergic contact dermatitis (1-4). Earlier studies have shown that 30-50% of all allergic reactions to cosmetics are due to perfume ingredients (1, 2), and that approximately 1% of the unselected population is sensitized to fragrances (5). A perfumer has thousands of fragrances available from which to compose a perfume, which may contain as many as 50 or more individual ingredients (6). This makes the diagnosis of perfume allergy complicated and screening agents such as the fragrance mix, balsam of Peru and, to some extent, colophony have been incorporated into the standard patch test series to overcome the problem. The detection of fragrance sensitization by mixes, the fragrance mix, and markers, balsam of Peru and colophony, means that no direct cause-effect relationship is established between the use of perfumed products, their content of different fragrance materials and allergic contact dermatitis.

The aim of the present study was to provide quantitative information about the content of certain sensitizing fragrance materials in cosmetic products that had caused skin reactions in fragrance-mix-positive patients, information that

may be considered in discussion of the clinical relevance of patch test reactions to this important screening agent for fragrance sensitization.

Materials and Methods

Patients and cosmetic products

11 eczema patients, 9 women and 2 men, undergoing patch testing at the Department of Dermatology, Gentofte Hospital, were selected for the study. The criteria of selection were cosmetic eczema, a positive patch test to the fragrance mix 8% pet., and a positive patch or use test to at least 1 perfumed leave-on cosmetic product currently used by the patient. A total of 23 cosmetic products gave a positive patch and/or use test (Table 1). In all cases, the use of these cosmetics completely or partly explained present or past episodes of eczema.

Patch and use tests

The patch tests were performed according to the ICDRG's recommendations (7). Scanpor® tape and Finn Chambers® were used. Readings were

Table 1. Patient characteristics and patch/use test results

Patient no.	Age (years)	Sex	Primary location of eczema	Product type	Product test	
					patch test	use test
1	39	F	neck	eau de perfume	+	NT
2	44	F	hands, face	body lotion	NT	positive D4
3	42	F	hands	eau de toilette	NT	positive D6
4	24	F	hands, axilla	deodorant	+	positive D3
				deodorant	+	NT
				deodorant	+	NT
5	39	F	face	eau de toilette	+	NT
				eau de toilette	+	NT
6	62	M	face, neck	aftershave	+	NT
				aftershave	+	NT
				aftershave	+	NT
				aftershave	+	NT
				hair lotion	+	NT
				deodorant	+	NT
				shaving gel	+	NT
7	23	F	neck, axilla	deodorant	NT	positive D3
8	22	M	hands	aftershave	+	NT
9	32	F	face, hands	eau de perfume	+	NT
10	16	F	hands	eau de toilette	+	positive D3
11	55	F	face	night cream	+	NT
				day cream	+	NT
				facial cream	+	NT
				facial cream	+	NT

F: female, M: male, NT: not tested. +: patch test reaction with erythema and infiltration.

done at D2 on removal of the patches, D3 and D5–7 using the ICDRG scale (7). The fragrance mix 8% (with 5% SSO) pet. from the European standard patch test series and its individual constituents were obtained from Hermal®, Reinbek, Germany. Cosmetic products available from the patients were patch tested as is. Use tests were done in the cubital fossa, 2–3 applications being made per day. The use test was considered positive when a persistent itchy rash appeared.

Analysis of fragrance materials in the cosmetic products

12 fragrance materials were selected for quantitative chemical analysis of the implicated cosmetics. The cosmetic products used in the analysis were purchased in the Danish retail market, as it was not possible to obtain samples of a satisfactory quality from the patients' own cosmetics. 87% of the products were international brands. The target fragrance materials included all 7 synthetic fragrance materials in the fragrance mix, citronellal and α -hexyl cinnamic aldehyde, which are chemically related to constituents of the fragrance mix, coumarin and citral, which have been reported as frequent sensitizers (8, 9) and dihydrocoumarin,

which is a sensitizer and banned from perfumes by IFRA (Table 2). Gas chromatography-mass spectrometry was used for the analysis of fragrance substances in the cosmetic products (10). The chemical analysis was performed independently and without knowledge of results from the clinical tests.

Results

Patch and use testing

The 23 products, subjected to chemical analysis, had given either a positive patch test (18 cases), a positive use test (3 cases) or both (2 cases) in a total of 11 patients with cosmetic eczema (Table 1). 5 of the products were creams/lotions, 6 were perfumes, 5 deodorants, 6 shaving products and 1 was a hair lotion (Table 1). The patients all had a positive patch test reaction to the fragrance mix 8% pet, and in 9 of the 11 patients patch testing with the individual constituents of the fragrance mix was done. At least 1 individual constituent elicited a patch test reaction in each of the 9 subjects (Table 4), including reactions with erythema only. In 4 patients, reactions to several constituents were found.

Table 2. Target fragrance materials

Substance	CAS no	Purity of standard	Source
geraniol	106-24-1	99.2%	Hermal
hydroxycitronellal	107-75-5	98.8%	Hermal
eugenol	95-53-0	99.6%	Hermal
isoeugenol	97-54-1	98.0%	Hermal
cinnamic aldehyde	14371-10-9	99.7%	Hermal
cinnamic alcohol	104-54-1	99.3%	Hermal
α -amyl cinnamic aldehyde	122-40-7	97.9%	Hermal
coumarin	91-64-5	crystalline	Aldrich
dihydrocoumarin	119-84-6	99%	Aldrich
citral	5392-40-5	95%	Aldrich
citronellal	106-23-0	85-90%	Sigma
α -hexyl cinnamic aldehyde	122-40-7	97%	Aldrich

Chemical analysis of the cosmetic products

The target fragrances in the cosmetics were analyzed with a detection limit of approximately 1 ppm, and the recovery of the target substances from the cosmetic products was >80%. The results of analysis of the selected fragrance materials in the cosmetic products are described in Table 3. All the products except one, a deodorant, were found to contain between 1 to 6 of the 7 synthetic fragrance materials in the fragrance mix (mean=3 constituents/products).

Hydroxycitronellal was present in 20 products and was the most often detected target substance, followed by eugenol, which was present in 17 products. Citral was found to be present in only one of the investigated products. Cinnamic aldehyde, dihydrocoumarin, and citronellal were not identified in any of the 23 products (Table 3). Besides these substances, a number of other fragrance materials were found frequently in the investigated products: limonene, diethyl phthalate, citronellol,

linalool, piperonal, phenylethyl alcohol, geranyl acetate, linalyl acetate, dihydromethyl jasmonate, benzyl acetate, benzyl benzoate, santholol, patchouli alcohol, methyl aminobenzoate and various sesquiterpenes (cinole, caryophellene, etc.)

Correlations between exposure and fragrance sensitivity

The correlation between patch test reactions to constituents of the fragrance mix and the presence of the substance concerned in the respective cosmetics is shown in Table 4. Thus the cosmetics of all patients who showed skin reactions to hydroxycitronellal, cinnamic alcohol, eugenol and α -amyl cinnamic aldehyde were found to contain the respective substances. The content of hydroxycitronellal was, on average, 0.18% in products used by hydroxycitronellal-sensitive patients and 0.032% in hydroxycitronellal-negative persons. Isoeugenol was present in cosmetics of 3 of the 4 cases with skin reactions to this substance, though at very low concentrations (<0.0010%), and 3 of these patients had patch test reactions to other constituents of the fragrance mix. Cinnamic aldehyde was not detected in any of the cosmetics used by the 3 patients sensitive to cinnamic aldehyde.

Discussion

Few studies link clinical data with quantitative exposure information. In the present study, patients with a cosmetic eczema, a positive patch and/or use test reaction to cosmetic products and a positive patch test reaction to the fragrance mix were included. The implicated cosmetics were analyzed and between 1 and 6 constituents from the fra-

Table 3. Content of target fragrance materials in the patch and/or use test-positive cosmetics

Substance	Concentration v/v % in 23 products		No. of products containing the substance
	range	mean	
hydroxycitronellal	<0.001-0.54	0.102	20
eugenol	<0.001-0.22	0.066	17
α -hexylcinnamic aldehyde	<0.001-0.66	0.127	15
coumarin	<0.001-0.2	0.083**	15
geraniol	<0.001-0.62	0.105*	12
cinnamic alcohol	<0.001-0.15	0.003**	12
α -amylcinnamic aldehyde	<0.001-0.32	0.066	7
isoeugenol	<0.001-0.03	0.009	6
citral	0.09	0.090	1
citronellal	ND		0
cinnamic aldehyde	ND		0
dihydrocoumarin	ND		0

The concentrations of fragrance substances identified at the 1-10 ppm level in cosmetic products are reported as <0.0010%.

* The substance present in another 3 products, where quantification was not possible due to interference.

**The substance present in 1 other product, where quantification was not possible due to interference.

ND: not detected; detection limit, approximately 0.0001%.

Table 4. Patch test reactions and exposure to 7 constituents of the fragrance mix

Constituent of the fragrance mix:	No. of persons with patch test reaction*	Sensitive cases exposed to the substance	Concentration of the substance in patch or use- test-positive cosmetics used by sensitive cases, v/v % range
geraniol	0/9	—	—
hydroxycitronellal	6/9	6/6	0.0045–0.5422
cinnamic alcohol	1/9	1/1	<0.0010–0.0094
eugenol	1/9	1/1	<0.0010–0.0517
isoeugenol	4/9	3/4	<0.0010
α -amyl cinnamic aldehyde	1/9	1/1	<0.0010–0.1163
cinnamic aldehyde	3/9	0/3	—

The concentrations of fragrance substances identified at the 1–10 ppm level in cosmetic products are reported as <0.0010%.

*Including reactions with erythema only.

grance mix were found in 22 out of 23 products. 9 of our patients were tested with the ingredients of the fragrance mix. The cosmetics of all the patients who showed skin reactions to hydroxycitronellal, eugenol, cinnamic alcohol and α -amylcinnamic aldehyde were found to contain the respective substances. 3 out of 4 patients with a patch test reaction to isoeugenol were exposed to it, but in low quantities <0.0010% (Table 4), which in itself would be expected to give skin symptoms only in highly sensitized individuals (11). 3 of the isoeugenol-sensitive patients reacted to several other constituents of the fragrance mix as well. Concomitant or simultaneous allergies are a well-known phenomenon in fragrance sensitization (12), and it may be that several substances in combination are required to exceed the limit for clinical symptoms, especially if the concentration of each substance is small (13–15).

Hydroxycitronellal was detected in 20 products. It is an important fragrance material to the perfumer and is widely used (16). Studies in the past 20 years have identified hydroxycitronellal as one of the most frequent sensitizers in patients with well-proven cosmetic eczema (1, 9) and in cosmetic products suspected of having caused skin problems (9). Results from use tests with hydroxycitronellal-containing products in experimentally sensitized humans contrast with these clinical data. Daily use of a soap bar containing a perfume with 0.05% hydroxycitronellal, and later a lotion with 0.03% hydroxycitronellal for several months, gave no clinical symptoms in 41 subjects previously sensitized to hydroxycitronellal by a human repeated insult patch test (17). When 31 of these subjects proceeded to use a cologne containing 0.05% hydroxycitronellal 3× daily for a month, 1 subject reacted (17). Another 3 subjects had a positive reaction after having used a cologne containing 1% hydroxycitronellal (17).

These results, however, may reflect more the sensitivity of the test panel than the safety of hydroxy-

citronellal-containing products. Contact sensitization is not an all-or-none phenomenon and the sensitivity of experimentally-sensitized individuals may be assumed to differ from the sensitivity of patients sensitized by everyday exposure to cosmetic products. Elicitation studies made for the purpose of safety assessment are only adequate if they include the target group for prevention, in this case persons with cosmetic eczema. The content of hydroxycitronellal was, on average, 0.18% in products used by hydroxycitronellal-sensitive patients and 0.032% in hydroxycitronellal-negative persons. All the patients had a cosmetic eczema associated with the use of the analyzed products, which also gave a positive patch and/or use test. The 5× difference in exposure concentrations between the sensitive and negative hydroxycitronellal patients may indicate a significant role for hydroxycitronellal in eliciting the skin reaction in the sensitive group. However, the patients may have had additional exposures from other cosmetics or household products used but not analyzed.

The constituents of the fragrance mix are well-proven allergens, yet the presence of other sensitizing fragrances or other allergens in the products may have contributed to the patients' disease. Most of the products analyzed were, however, perfumes, deodorants or aftershaves, which may be expected to contain few other significant sensitizers apart from the fragrance materials (18). In addition, none of the patients were sensitized to frequently used preservatives, which are also common causes of contact allergy to cosmetics (19).

Oak moss is a frequent fragrance sensitizer (12) and 5 of our patients had patch test reactions to this substance. No attempt was made to analyze the content of oak moss in the cosmetics, as it is a natural compound that may contain several yet unknown sensitizing substances, making quantitative exposure assessment pointless. 4 of the oak-moss-sensitive cases also reacted to other constituents of the fragrance mix.

Cinnamic aldehyde has been one of the most frequently reported fragrance allergens (20). 3 of our patients were sensitive to this substance, but cinnamic aldehyde was not found in any of the 23 analyzed products. Cinnamic alcohol, which may be metabolized in the skin to cinnamic aldehyde (21), was found in 12 products, including the products of the 3 patients sensitive to cinnamic aldehyde. Furthermore, the structurally similar alfa-amyl cinnamic aldehyde and alfa-hexyl cinnamic aldehyde were found in many products (Table 3). It is thus possible that cinnamic aldehyde is a marker of sensitization to other related substances, or that the patients had been sensitized in the past or used products containing cinnamic aldehyde, which were not analyzed in the current study.

Due to its sensitizing properties, the use of dihydrocoumarin as a fragrance material has been discouraged by the International Fragrance Association since 1974. Dihydrocoumarin was detected in 10 out of 31 products in a previous study (10), but not in any of the currently investigated products.

In this study, it is demonstrated that exposure to constituents of the fragrance mix is common in fragrance-allergic patients with cosmetic eczema. The exposure was seen to cover a large range of concentrations, but also sometimes to be rather intense. Several constituents of the fragrance mix were often found in the same product, suggesting that the fragrance mix is a good reflection of actual exposure. An association has been established between exposure and symptoms, and, even though the cross-sectional design of the study limits our conclusions, the results obtained have implications for assessment of the clinical relevance of patch test reactions to the fragrance mix, and for future strategies for safety testing of perfumed products.

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